

Randomized controlled trial data for successful new
drug application for rare diseases

Yosuke Kubota

DP20402

Department of Clinical Medicine (Pharmaceutical Medicine)

Graduate School of Pharmaceutical Sciences

Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo, 108-8641, Japan

Abstract

Background:

Rare diseases pose a significant issue as effective treatments are often not available due to their small number of patients, and unclear causes and progression mechanisms. Development of drugs for rare disease (orphan drugs) is an urgent challenge considering the substantial unmet medical needs. However, orphan drug development has several limitations, including a lack of sufficient information and difficulty in conducting clinical trials due to the small number of patients. In general, for clinical trials, a randomized controlled trial (RCT) is considered the gold standard. Health authorities such as the United States (US) Food and Drug Administration and European Medicines Agency emphasize the importance of scientific evidence and recommend RCTs as one of important trial designs. RCT has potential to minimize bias and generate high-quality data, but it involves a higher cost. Single-arm trial (SAT), on the other hand, is relatively cost-effective due to its single-group design, and it promotes patient enrollment by ensuring access to the active treatment arm. However, it is essential to be cautious about the potential impact of various biases associated with SATs. Pharmaceutical companies often hesitate to make substantial investments of costs and time in orphan drug development due to the low likelihood of investment returns, especially when RCTs require a large number of patients. In light of these circumstances, in practice, implementation of RCTs

in orphan drug development has been reported to be low, suggesting room for flexibility in data required for regulatory approval. The aim of this research was to investigate the potential factors associated with the need for RCT data in the clinical data package for new drug application (NDA) of orphan drugs, by evaluating the state in Japan (Research 1) and the US (Research 2).

Methods:

Research 1 focused on 130 new drugs with orphan drug designation approved in Japan between April 2004 and March 2020. Research 2 focused on 233 new drugs with orphan drug designation approved in the US between April 2001 and March 2021. In both research, after collecting information on factors potentially related to the judgement on the necessity of RCT data, univariable and multivariable logistic regression analyses were conducted to investigate the association between the presence or absence of RCT data in the clinical data package for NDA and those factors.

Result:

In Research 1, approximately two-thirds of the orphan drugs (87 out of 130) included a pivotal RCT in their clinical data package, while one third (43 out of 130) relied on a pivotal SAT. Univariable analyses showed that the presence or absence of RCT data in the clinical data package for NDA in Japan was associated with (1) disease prevalence in

Japan and (2) type of primary endpoint. The result of the multivariable logistic regression analysis showed that disease prevalence in Japan (odds ratio [OR] 3.21, 95% confidence interval [CI] 1.18–8.6) and type of primary endpoint (OR 6.66, 95% CI 2.41–18.37) were associated with the presence or absence of RCT data in the clinical data package in Japan. In Research 2, approximately two-thirds of orphan drugs (151 of 233) had a pivotal RCT, and one third (82 of 233) had a pivotal SAT in the clinical data package. Univariable analyses showed that the following factors were associated with the presence or absence of RCT data in the clinical data package for NDA in the US: (1) severity of the disease outcome, (2) type of drug usage, and (3) type of primary endpoint. The results of the multivariable logistic regression analysis showed that the severity of the disease outcome (OR 5.63, 95% CI 2.64–12.00), type of drug usage (OR 2.95, 95% CI 1.80–18.57), and type of primary endpoint (OR 5.57, 95% CI 2.57–12.06) were associated with the presence or absence of RCT data.

Conclusion:

Our results indicated that the presence or absence of RCT data in the clinical data package for successful NDA of orphan drugs was associated with several factors: disease prevalence, severity of the disease outcome, type of drug usage, and type of primary endpoint. Especially, type of primary endpoint was consistent in both Japan and the US.

Even in the development of orphan drugs, it has been suggested that the emphasis should be placed on the formulation of strategies grounded in the scientific evaluation of the investigational drug and the target disease, rather than solely on the feasibility of conducting trials based on the small number of patients. To optimize development strategies and investment, it is advisable for companies to conduct thorough assessment of clinical development plan at the beginning based on the accurate collection and analysis of foundational information. We hope our research will contribute to optimize the drug development plan through enhancing the predictability of the necessity of RCT data for NDA and also encourage strategic collection of the target disease information to promote future orphan drug development.

Table of Contents

Abstract	i
Table of Contents	v
List of Tables	vi
List of Figures	vii
Abbreviations	viii
1. Introduction	1
2. Research 1	7
2.1 Objectives	7
2.2 Method	8
2.3 Result	12
2.4 Discussion	17
3. Research 2	22
3.1 Objectives	22
3.2 Method	23
3.3 Result	25
3.4 Discussion	30
4. Overall Discussion	34
5. Conclusion	38
References	39
Acknowledgement	46
Appendix 1	47
Appendix 2	48

List of Tables

Table 1 Characteristics of orphan drugs (Japan)

Table 2 Result of univariable and multivariable logistic regression analysis (Japan)

Table 3 Characteristics of orphan drugs (US)

Table 4 Result of univariable and multivariable logistic regression analysis (US)

List of Figures

Figure 1 Long-tailed distribution of rare diseases with different prevalence

Figure 2 Hierarchy of evidence in medicine

Figure 3 Flow diagram of drug selection (Japan)

Figure 4 Flow diagram of drug selection (US)

Abbreviations

ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
EMA	European Medicines Agency
FDA	US Food and Drug Administration
MHLW	Ministry of Health, Labour and Welfare
MRCT	Multi Regional Clinical Trial
NDA	New Drug Application
ODD	Orphan Drug Designation
OR	Odds Ratio
PMDA	Pharmaceuticals and Medical Devices Agency
RCT	Randomized Controlled Trial
SAT	Single Arm Trial
US	United States of America
WHO	World Health Organization

1. Introduction

Nearly 7,000 rare diseases have been identified worldwide[1], forming a long-tailed distribution with different prevalence (**Figure 1**). Rare diseases pose a significant issue as effective treatments are often not available due to the unclear causes and progression mechanisms [2]. To tackle the challenges associated with development of drugs for rare disease, various governments have established incentives, such as prioritized review of development products and tax benefits, to promote it [1,3]. As of 2019, 724 drugs received at least one associated approval with orphan drug designation (ODD) in the United States (US) [4]. In Japan, 322 drugs have been approved with ODD as of 2018 [5]. The trend of increasing ODDs and approvals is evident in both countries and also in Europe , reflecting positive global trends [6]. However, despite the tremendous efforts made by academia, pharmaceutical companies, and regulatory agencies, there are still significant unmet medical needs. The discovery and development of effective treatments for rare diseases are pressing needs [7].

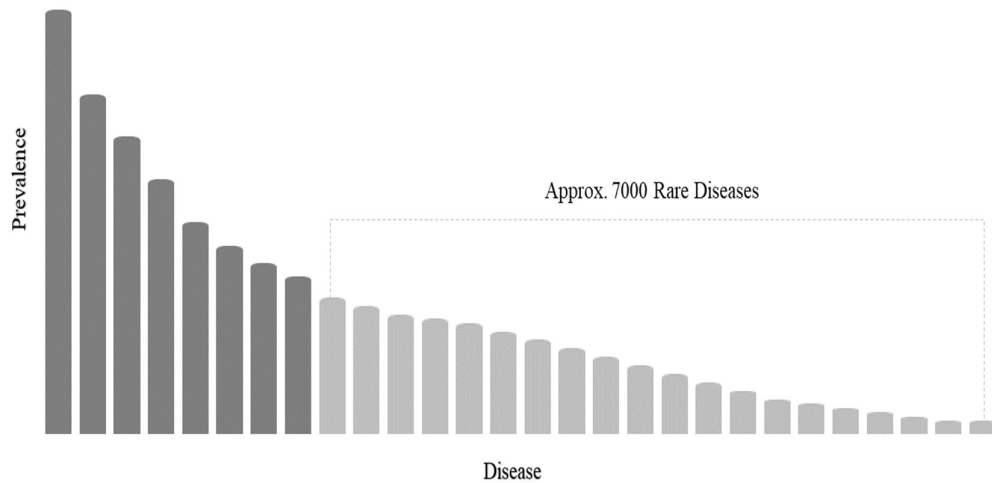


Figure 1 Long-tailed distribution of rare diseases with different prevalence

(Source: modified from the figure in STAR Therapeutics website,
<https://star-therapeutics.com/setting-our-sights-on-the-long-tail-of-disease/>)

When exploring the specific challenges related to conducting clinical trials for orphan drug development, there are several limitations because of the small patient population. Clinical trials for rare diseases tend to be uncertain which could be attributed to the weak protection against type 1 and type 2 errors or to inappropriate designs for understanding the causality of treatment interventions [8]. Among the various features of clinical trial design, randomization of patients is of key importance to prevent selection bias [9–11]. Traditional randomized controlled trials (RCTs), with two or more parallel arms, fixed sample size, and adequately powered statistical threshold for significant differences, are widely accepted as the scientific gold standard. The results of RCTs provide evidence of

the highest grade in the hierarchy of research designs [12] (**Figure 2**). Nevertheless, RCTs are costly and less feasible for orphan drug development because of the small target population, heterogeneity of patients, and ethical considerations related to the rarity of the disease [13]. Several designs and methods, such as a crossover RCT, an adaptive RCT, and Bayesian analysis, have been proposed to optimize and facilitate clinical development in the field of rare diseases [14–19]. For example, a crossover RCT has several advantages including enhanced recruitment, since each participant is guaranteed exposure to the study treatment, and a perfect balance of baseline characteristics; however, appropriate measures to avoid carryover effects or dropouts are required [15,17].

Some clinical trials of rare diseases have been conducted with a single-arm, before-after comparison design. The single-arm trial (SAT) has certain advantages over an RCT, such as a smaller sample size and guaranteed exposure to the study treatment. However, it entails a risk of various forms of biases due to the lack of a comparator group. Utilization of real-world data is drawing attention to help mitigate these rare disease-specific issues [20–22]

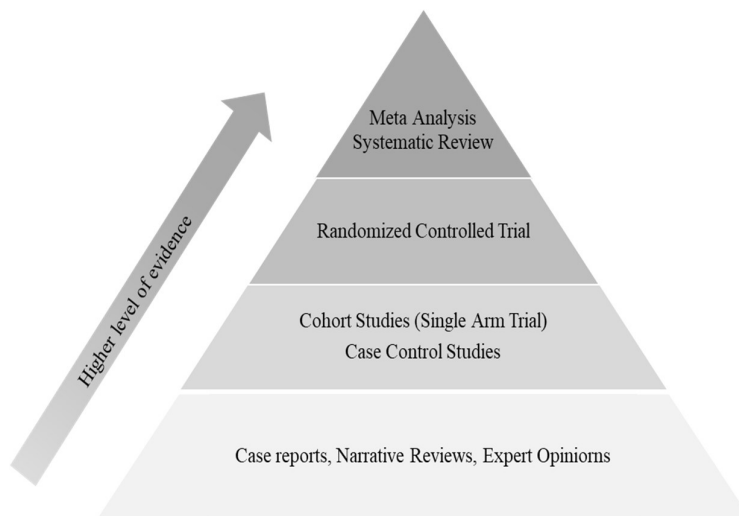


Figure 2 Hierarchy of evidence in medicine

(Source: modified from Figure 2 in Chugai Pharmaceutical Co., Ltd website, <https://chugai-pharm.jp/ma/research-and-medical/clinical-research/real-world-study-1/>)

From a regulatory standpoint, guidelines from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) emphasize the importance of scientific evidence in evaluating the efficacy of orphan drugs while acknowledging these complexities in rare diseases [23,24]. In the guidelines, RCTs are recommended as one of the methods for generating high-level evidence data. At the same time, the incorporation of information beyond clinical trials, such as natural history study data, research reports, and the use of real-world data, to generate comprehensive evidence is also drawing attention [20-22]. Reflecting this reality, it has been reported that clinical trials for rare diseases tended to have fewer RCTs than those for non-rare diseases [23]. This suggests

that there is some flexibility in the clinical data required for new drug application (NDA).

Pharmaceutical companies and regulatory authorities formulate an optimal orphan drug development strategy that takes into account the necessary quality and quantity of evidence. The feasibility of clinical trials for rare diseases is also discussed on a case-by-case basis.

Considering these circumstances, this research aimed to address the question: "Under what circumstances are RCT data required in the orphan drug development?".

Previous research in various regions, including Japan, the US, and Europe, has conducted an analysis of the clinical data packages for orphan drugs [8,27,28]. In these research, as mentioned earlier, the limited availability of RCTs, the limited total number of enrolled patients, and variations in trial design selection based on disease characteristics were pointed out, highlighting the uniqueness of orphan drug development. However, to the best of our knowledge, no detailed research has been conducted regarding the factors associated with the requirement of RCT data in orphan drug development.

The purpose of this research was to investigate factors related to the necessity of RCT data included in clinical data packages submitted for NDA of orphan drugs, which is a crucial element in generating high-level evidence and can impact on the company's

strategy. The research initially focused on the clinical data package in Japan, subsequently shifted the focus on that in the US, where new drug development is most actively pursued.

2. Randomized controlled trial data for new drug application for rare diseases in Japan (Research 1)

2.1 Objectives

In recent years, academia, pharmaceutical companies, and regulatory agencies have dedicated significant efforts to address the challenges of rare diseases. However, significant unmet needs for new medicines still exist. Clinical trials for rare diseases face limitations primarily due to their small sample sizes. A large-scale survey has shown that compared to non-rare diseases, trials for rare diseases are less likely to incorporate blinding and randomization [8].

Randomization of study subjects is a critical aspect of clinical trial design, serving as a key measure to prevent selection bias [9-11]. Traditional RCTs, characterized by two or more parallel arms, a fixed sample size, and appropriately powered statistical thresholds for significant differences, are widely regarded as the scientific gold standard. The results of RCTs provide the highest level of evidence in the hierarchy of research designs [12]. However, it's important to note that RCTs are costly and, therefore, less practical for orphan drug development. On the other hands, some clinical trials of rare diseases have been conducted with a single-arm, before-after comparison design. The SAT has certain

advantages over an RCT, such as a smaller sample size and guaranteed exposure to the study treatment. Nonetheless, it entails a risk of various forms of biases due to the lack of a comparator group. Under these considerations, in Japan, the development of orphan drugs requires various arrangements in the clinical trial design such as efficacy endpoints, controls, and determination of sample size [27]. The objective of this research was to examine the potential factors associated with the necessity of an RCT in a clinical data package for orphan drugs in Japan to facilitate future drug development for rare diseases.

2.2 Method

2.2.1 Data source and items

Newly approved drugs with an ODD between April 2004 and March 2020 in Japan were extracted from the approved drug list on the website of the Pharmaceuticals and Medical Devices Agency (PMDA) (<https://www.pmda.go.jp/PmdaSearch/iyakuSearch/>).

Among them, drugs for surgery aid and vaccines were excluded, to focus on treatment drugs. In addition, drugs that were approved without any clinical trial data were excluded due to lack of information.

Further, for each approved drug, a pivotal trial, typically a clinical trial to confirm the safety and efficacy of the drug, was selected from the PMDA review report. This selection

was done based on the following hierarchy: trial phase (phase 3, 2), trial design (RCT, SAT), and number of enrolled patients (large, small). The pivotal trial design was categorized as an RCT or a SAT. If several indications were approved in a single NDA based on different pivotal trials, each indication was treated as a distinct approval. The following data were extracted for the selected drugs: approval year, disease prevalence in Japan, company nationality, modality, drug usage, prior approval outside of Japan, Anatomical Therapeutic Chemical (ATC) classification [29], availability of alternative treatment(s) in Japan, severity of the disease outcome, development request from the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Needs (the Committee) [30], target age segment, and type of primary endpoint in the selected pivotal trial.

When assessing the potential association with the presence or absence of an RCT or a SAT in the clinical data package as a response variable, we selected factors that could be potentially associated with it, while minimizing the number of explanatory variables to ensure the reliability of the regression analysis [31, 32]: disease prevalence in Japan ($1 < 100,000$ vs. $\geq 1/100,000$ patients), severity of the disease outcome (high mortality vs. others), development request from the committee (no vs. yes), therapeutic classification

(oncology vs. non-oncology), target age segment (children with or without adult vs. adult only), and type of primary endpoint (biomarker vs. clinical outcome).

Severity of the disease outcome was categorized as high mortality or others (e.g., progressing disability early in life resulting in fatal outcome, or chronic but manageable with treatments and lifestyle adjustments, indicating non-fatal characteristics). We categorized the severity of the disease outcome into high mortality or others based on the information available on the review reports, Information Center for Specific Pediatric Chronic Diseases, Japan website (<https://www.shouman.jp/>), and Japan Intractable Diseases Information Center website (<https://www.nanbyou.or.jp/>). Subsequently, some of the high mortality diseases were changed to others, based on whether the mortality is manageable with alternative treatment(s), to reflect the impact of available alternative treatment(s) on the severity of disease outcome in Japan.

The type of primary endpoint of the selected pivotal trial was categorized as a biomarker or a clinical outcome. For the categorization, we referred to the Pharmacodynamic /Response biomarker definition: *“A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent”* and the clinical outcome definition: *“An outcome that describes or*

reflects how a patient feels, functions, or survives” [33]. In the case of multiple primary endpoints, the clinical outcome was preferentially selected.

We independently assessed these two explanatory variables. Disagreements between the reviewers were resolved by consensus and a 100% consensus was reached for all the data included in the analysis.

The development request by the Committee was categorized as “no” or “yes.” Usually, the Committee, launched by the Ministry of Health, Labour and Welfare (MHLW), evaluates whether a proposed drug would meet the high medical needs for the target disease, including rare diseases, and makes development requests to pharmaceutical companies [30]. The Committee’s requested information was collected from its website (https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00001.html or https://www.mhlw.go.jp/stf/shingi/other-iyaku_128702.html).

The definition and criteria of other explanatory variables are summarized in **Appendix 1** (supplementary information).

2.2.2 Statistical analysis

The associations between the response variable and each of the explanatory variables were assessed using univariable and multivariable regression analysis to calculate the

crude odds ratio (OR) and 95% confidence interval (CI). In the multivariable regression analysis, we have removed therapeutic classification (oncology vs. non-oncology) from the explanatory variables, because it showed high association with the severity of the disease outcome in Cramer' V (Cramer' V > 0.5). Other explanatory variables did not show high association with each other and were included in the multivariable regression analysis. Statistical significance was set at $P < 0.05$. StatsDirect version 3.3.3 software was used for all statistical analyses.

2.3 Result

A total of 144 drugs with ODD were identified from 491 newly approved drugs between April 2004 and March 2020 in Japan. Among these, 130 drugs with ODD were selected for analysis (**Figure 3**).

The characteristics of the selected orphan drugs were summarized along with the design of the pivotal trial, an RCT or SAT (**Table 1**). Approximately two-thirds of the orphan drugs (87 of 130) had a pivotal RCT, and one-third (43 of 130) had a pivotal SAT in the clinical data package. Most of the drugs (115 of 130) were approved outside Japan when the NDA was filed in Japan; the Committee had requested for the development of about one-third of the drugs (42 of 130) in Japan. Sixty-four percent of the orphan drugs with an RCT had alternative treatment(s) for the target disease, while 39.5% of the drugs with

a SAT had alternative treatment(s).

Table 2 shows the result of the univariable and multivariable analysis to investigate the associations between the presence or absence of RCT data in the clinical data package and the explanatory variables. Univariable analyses revealed that the presence or absence of RCT data in the clinical data package for an NDA in Japan was associated with the following factors: (1) disease prevalence in Japan and (2) the type of primary endpoint. The result of the multivariable analysis also suggested that the disease prevalence in Japan (OR 3.21, 95% CI 1.18–8.6) and the type of primary endpoint (OR 6.66, 95% CI 2.41–18.37) were associated with the presence or absence of RCT data.

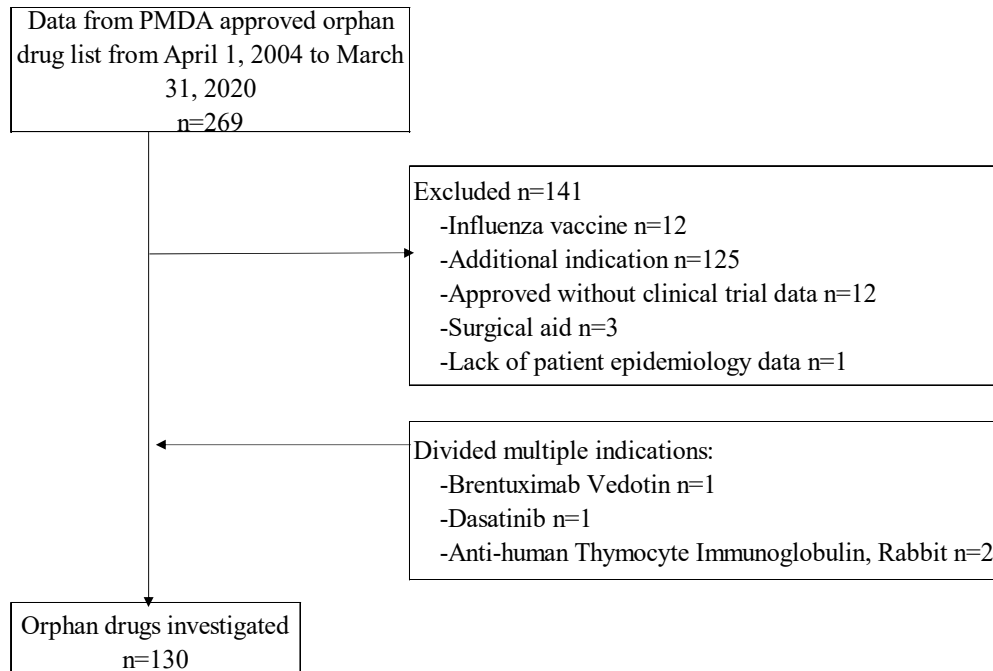


Figure 3 Flow diagram of drug selection (Japan)

PMDA: Pharmaceuticals and Medical Devices Agency

Table 1 Characteristics of orphan drugs (Japan)

Factor	RCT (n=87)	SAT (n=43)	Total (n=130)
Approval year			
2004-2008	24 (27.6%)	9 (20.9%)	33
2009-2013	20 (23.0%)	13 (30.2%)	33
2014-2020	43 (49.4%)	21 (48.8%)	64
Disease prevalence in Japan			
1-5 / 10,000	4 (9.3%)	24 (27.6%)	28
1-9 / 100,000	21 (48.8%)	46 (52.9%)	67
1-9 / 1,000,000	11 (25.6%)	6 (6.9%)	17
<1 / 1,000,000	7 (16.3%)	11 (12.6%)	18
Company nationality			
Japanese	24 (27.6%)	21 (48.8%)	45
Foreign affiliated	63 (72.4%)	22 (51.2%)	85
Modality			
Chemical	60 (69.0%)	26 (60.5%)	86
Biologics	27 (31.0%)	17 (39.5%)	44
Drug usage			
Mono therapy	73 (83.9%)	43 (100%)	116
Combination therapy	14 (16.1%)	0	14
Prior approval outside of Japan			
Yes	82 (94.3%)	33 (76.7%)	115
No	5 (5.7%)	10 (23.3%)	15
ATC code			
A (Alimentary tract and metabolism)	12 (13.8%)	7 (16.3%)	19
B (Blood and blood forming organs)	5 (5.7%)	4 (9.3%)	9
C (Cardiovascular system)	3 (3.4%)	3 (7.0%)	6
G (Genito urinary system and sex hormones)	0	1 (2.3%)	1
H (Systematic hormonal preparations, excl. sex hormones and insulins)	0	1 (2.3%)	1
J (Antiinfectives for systemic use)	15 (17.2%)	0	15

L (Antineoplastic and immunomodulating agents)	42 (48.3%)	26 (60.5%)	68
M (Musculo-skeletal system)	1 (1.1%)	0	1
N (Nervous system)	6 (6.9%)	1 (2.3%)	7
R (Respiratory system)	1 (1.1%)	0	1
S (Sensory organs)	2 (2.3%)	0	2
Alternative treatment in Japan			
Not available	31 (35.6%)	26 (60.5%)	57
Exists	56 (64.4%)	17 (39.5%)	73
Severity of the disease outcome			
High mortality	43 (49.4%)	27 (62.8%)	70
Others	44 (50.6%)	16 (37.2%)	60
Development request from the Committee			
No	62 (71.3%)	26 (60.5%)	88
Yes	25 (28.7%)	17 (39.5%)	42
Target age segment			
Children with or without adult	19 (21.8%)	15 (34.9%)	34
Adult only	68 (78.2%)	28 (65.1%)	96
Primary efficacy endpoint			
Pharmacodynamic/Response biomarker	42 (48.3%)	35 (81.4%)	77
Clinical outcome	45 (51.7%)	8 (18.6%)	53

Table 2 Result of univariable and multivariable regression analysis (Japan)

Factor	RCT (n=87)	SAT (n=43)	Total (n=130)	Univariable regression analysis			Multivariable regression analysis		
				Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Prevalence in Japan									
<1/100,000	17 (19.5%)	18 (41.9%)	35	Reference			Reference		
≥1/100,000	70 (80.5%)	25 (58.1%)	95	2.72	1.22-6.07	0.0149*	3.21	1.18-8.6	0.0226*
Severity of the disease outcome									
High mortality	43 (49.4%)	27 (62.8%)	70	Reference			Reference		
Others	44 (50.6%)	16 (37.2%)	60	1.30	0.49-3.43	0.5941	1.48	0.64-3.45	0.3604
Development request from the Committee									
No	62 (71.3%)	26 (60.5%)	88	Reference			Reference		
Yes	25 (28.7%)	17 (39.5%)	42	0.62	0.28-1.32	0.2172	0.60	0.24-1.5	0.2745
Target age segment									
Children with or without adult	19 (21.8%)	15 (34.9%)	34	Reference			Reference		
Adult only	68 (78.2%)	28 (65.1%)	96	1.92	0.86-4.30	0.1141	1.62	0.57-4.69	0.3662
Primary efficacy endpoint									
Pharmacodynamic/Response biomarker	42 (48.3%)	35 (81.4%)	77	Reference			Reference		
Clinical outcome	45 (51.7%)	8 (18.6%)	53	4.69	1.95-11.3	0.0005*	6.66	2.41-18.37	0.0003*
Therapeutic classification									
Oncology	29 (33.3%)	22 (51.2%)	51	Reference			N/A		
Non-oncology	58 (66.7%)	21 (48.8%)	79	2.10	0.99-4.42	0.0519			

**P* value < 0.05

2.4 Discussion

Among the various features of clinical trial design, randomization of trial subjects is of key importance to minimize bias [9-11].

Occasionally, the feasibility of RCT is potentially impacted by factors including but not limited to the patient population that are able to be enrolled and studied, disease severity, treatment landscapes of available therapies, reliability of assessment items, external comparator data, understanding about the natural history of the disease, and the existence of clinical equipoise [34]. The very limited number of eligible patients, unrevealed natural history of the disease, and heterogeneity make it difficult to conduct appropriate RCTs.

To cope with these challenges, orphan drug development in Japan often utilizes foreign clinical data to support an NDA based on multiregional clinical trial or bridging strategy [35]. The PMDA and pharmaceutical companies determine the optimized clinical data package in Japan by considering the feasibility of development, robustness of evidence, and the unique unmet medical needs for each rare disease. Therefore, most clinical data packages examined in this research included Japanese and foreign data, with the exception of few special cases of anti-HIV drugs, which were approved only with foreign clinical data. We investigated the details of the required clinical data package for orphan drugs in Japan with the aim of identifying potential factors associated with the presence or absence of RCT data.

Two factors were associated with the presence or absence of RCT data in the NDA package in Japan. One factor was the disease prevalence in Japan. A higher disease prevalence was positively associated with the presence of RCT data.

This was expected, because the feasibility of a clinical trial is impacted by the patient

population that can be potentially enrolled and studied. From the Japanese clinical data package perspective, it indicates the common issue between the PMDA and pharmaceutical companies for NDA submission. We believe that the PMDA and pharmaceutical companies should discuss the suitability of RCT or SAT data, regardless of whether the trial is Japanese or not, by considering the unique factors such as the number of patients and the unmet medical needs in Japan. There is a lower proportion of trials with standard methodological approaches, such as blinding and randomization, for orphan drug development [23]. The RCT data is often absent in the clinical data package of ultra-orphan drugs in Japan [27]. Our results are in line with that from earlier reports. The second factor was the type of primary endpoint in the pivotal trial. The use of clinical outcome as a primary endpoint was positively associated with the presence of RCT data. In general, even for rare diseases, regulatory approval requires the demonstration of clinical benefit, defined as how a patient feels, functions, or survives [36]. A guidance document for rare diseases by the US FDA states that “Despite continuing efforts to develop novel surrogate endpoints, currently, clinical outcomes as opposed to surrogate endpoints are the usual endpoints for the adequate and well-controlled trials” [24]. However, often the disease course is not well understood, and the appropriate disease-specific endpoints and assessment measures seldom exist for rare diseases. The clinical investigation of new endpoints is useful in earlier trials; however, these endpoints often have no regulatory precedent. In addition, large variability in the potential effect size in clinical assessment requires a sizable sample size; this makes the conduct of RCTs difficult for rare diseases. Biomarkers are usually used as supportive secondary endpoints in later stages of development along with a clinical primary endpoint. Biomarkers do not directly measure clinical outcomes and require proper verification and validation, such as

a correlation with key clinical symptoms or a true endpoint. The changes in biomarkers may not translate into clinical benefits due to the complex nature of the disease.

Nevertheless, biomarkers may be helpful in reducing the sample size and the assessment duration, because their change is often quick, more objective, and is measured more reliably than clinical outcomes. For these reasons, the type of endpoint, a clinical outcome, or a biomarker, could be associated with the conduct of RCTs within the various constraints of orphan drug development.

A primary endpoint is a key consideration in designing a clinical trial; however, a comprehensive efficacy assessment along with other secondary and exploratory endpoints is important for the overall assessment of orphan drugs [24,25]. It is crucial to determine an appropriate primary endpoint through discussions between the health authority(ies) and the pharmaceutical company. Various factors are taken into consideration to determine the appropriate endpoints; these include the natural history of the disease (e.g., etiology, pathological factors, homogeneity of the disease, acute or chronic), regulatory precedents, trial feasibility, availability of appropriate biomarkers, and other established efficacy assessment tools. In general, the optimal endpoint to assess the ameliorating effects of the target disease is used in a pivotal trial. This research highlights the importance of a thorough discussion on the endpoint. A SAT could be justified if an appropriate biomarker is available for the target rare disease. This could result in the absence of RCT data in the clinical data package in Japan, regardless of where the pivotal trial was conducted.

We presumed that the severity of the disease outcome would show association with the absence of RCT data, due to ethical concerns pertaining to placebo-controlled trials in some cases [44]; however, no statistically significant result was observed (**Table 2**).

Therefore, more associations between the disease prevalence and type of primary endpoint with an RCT implies the importance of scientific evidence and clinical trial feasibility in a small population, even though the severity of the disease outcome has high mortality.

We believe that the drug usage, either monotherapy or combination therapy, is a potential factor of RCT feasibility. We identified 14 drugs that were tested as a combination therapy with the available treatment; all of them were in RCTs. No drug was tested as a combination in SATs. Therefore, the existence of baseline treatment for the target disease could decrease the ethical burden of RCTs; however, we could not evaluate the association statistically.

A deep understanding of the natural history of the target disease could contribute to determining the feasibility or necessity of an RCT. In case of rare diseases, it is often difficult to have enough knowledge on the natural history; the scientific arguments for drug development rely on academic research, registry database, or retrospective/prospective natural history study. The utilization of real-world data as an external comparator of a SAT is drawing attention [20-22]. The existence of reliable external control data is a strong driver to justify a SAT; however, it was difficult to uniformly quantify the contribution of various types of natural history evidence. This is a limitation of this research.

Clinical equipoise is an important ethical consideration for determining the feasibility of RCTs, including in cases where additional trials are conducted in Japan for drugs that have already been approved in other countries. Clinical equipoise is the idea that there is uncertainty with the merits of a specific intervention in a clinical trial compared to that of the alternative treatment arm [34]. Clinical equipoise is unbalanced to justify the conduct

of RCTs, if an earlier trial of the program showed a significant signal in efficacy and/or safety of the test drug. It might be ethically difficult to conduct RCTs under such situations. It was difficult to uniformly quantify the equipoise over the various areas of the drugs, for investigating its association with the presence or absence of RCT data; we consider this a limitation of this research. There is active argument surrounding this concept; however, there is no universally accepted criteria for its implementation [45].

This research has several other limitations. First, it was conducted only for approved drugs, which could be regarded as a source of bias. The information available on negative results is less extensive than that for approved drugs. Second, the data were collected only for drugs that had an ODD before receiving marketing authorization by the MHLW. Drugs without an ODD were excluded, although they might have met the ODD criteria.

Finally, in this research, we restricted to the clinical data package in Japan to assess development strategies that include local and foreign trials. Similar investigations in other regions are required in the future.

Whenever possible, standard methodological approaches should be applied in the design and analysis of clinical trials [46]. However, in orphan drug development, there are instances when the number of experimental subjects is unavoidably small. In such cases, it would be reasonable to decide the drug approvals based on the available evidence. We believe it is worth investigating potential factors, including those reported in this research; they would help optimize and facilitate orphan drug development.

3. Randomized controlled trial data for successful new drug application for rare diseases in the United States (Research 2)

3.1 Objectives

In the US, rare diseases are defined as "diseases with fewer than 200,000 patients in the US" [38]. It is estimated that there are approximately 7,000 rare diseases worldwide, and approximately 30 million people in the US are afflicted with a rare disease [1,3]. The US government has supported the development of orphan drugs since 1983 [39]. Currently, the exclusivity period is set at seven years, 50% of the costs are tax-deductible, and a new drug application fee to the USFDA is exempt [40].

Despite these efforts, the lack of disease information, difficulty in patient recruitment, and demanding regulatory requirements for new drug reviews have been highlighted as hurdles to further accelerate developing orphan drugs. In many cases, patients are scattered across the country or region, specialized medical institutions are not always located nearby, and accurate diagnosis takes time, which makes conducting clinical trials difficult. However, regulatory authorities recommend generating as much high-quality evidence as possible under such circumstances [24,25,41].

Pharmaceutical companies and regulatory authorities are actively engaged in crafting optimal orphan drug development strategies. These strategies take into account the quality and quantity of evidence required on a case-by-case basis. There is growing attention towards incorporating information beyond clinical trials. This includes data from natural history studies, research reports, and real-world data, with the goal of creating comprehensive evidence that accounts for the various biases encountered [20-22]. In any case, RCTs remains one of the most important elements in discussing high-quality evidence [9-11]. As described above, the utilization of RCT data is considered to have

important implications also for orphan drug development.

The objective of this research was to examine the potential factors associated with the necessity of an RCT in a clinical data package for orphan drugs in the US to facilitate future orphan drug development.

3.2 Method

3.2.1 Data source and items

Newly approved drugs with an ODD in the US between April 1, 2001, and March 31, 2021, were extracted from the approved drug list on the website of the US FDA (<https://www.accessdata.fda.gov/scripts/opdlisting/ood/>). Among them, drugs with missing patient prevalence data, drugs for diagnosis or surgery aid, and drugs that were approved without clinical trial data were excluded from the analysis.

Furthermore, for each approved drug, a pivotal trial, typically a clinical trial to confirm the safety and efficacy of the drug, was selected from the US FDA review report. This selection was performed based on the following hierarchy: trial phase (phase 3, 2), trial design (RCT, SAT), and the number of enrolled patients (large, small). The pivotal trial design was categorized as RCT or SAT. If several indications were approved in a single NDA based on different pivotal trials, each indication was treated as distinct approval. The following data were extracted for the selected drugs: approval year, prevalence of the target disease, modality, ATC classification [29], target age segment, type of primary endpoint in the selected pivotal trial, severity of the disease outcome, prior approval outside the US, availability of alternative treatment(s) in the US, type of drug usage (mono or combination therapy), and designations of special regulatory pathways in the US (fast track, breakthrough therapy, priority review, and accelerated approvals).

When assessing the potential association with the presence or absence of an RCT in the clinical data package as a response variable, we selected factors that could be potentially associated with it, while minimizing the number of explanatory variables to ensure the reliability of the regression analysis [31,32]: disease prevalence ($< 1/100,000$ vs. $\geq 1/100,000$ patients), severity of disease outcome (high mortality vs. others), type of drug usage (monotherapy vs. combination therapy), therapeutic classification (oncology vs. non-oncology), target age segment (children with or without adult vs. adult only), and type of primary endpoint (biomarker vs. clinical outcome).

The severity of the disease outcome was categorized as high mortality or others (e.g., progressing disability early in life resulting in fatal outcome, or chronic but manageable with treatments and lifestyle adjustments, indicating non-fatal characteristics) based on the information available on the review reports and the Orphanet website (<https://www.orpha.net/consor/cgi-bin/index.php>). Subsequently, some of the high-mortality diseases were changed to others, based on whether the mortality was manageable with alternative treatments, to reflect the impact of the available alternative treatments on the severity of disease outcome in the US.

The primary endpoint of the selected pivotal trial was categorized as a biomarker or clinical outcome. We referred to the pharmacodynamic or response biomarker definition, “a biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.” Clinical outcome was defined as “an outcome that describes or reflects how a patient feels, functions, or survives [30].” In case of multiple primary endpoints, clinical outcomes were preferentially selected.

We assessed these two explanatory variables independently. Disagreements between the

reviewers were resolved by consensus, and a 100% consensus was reached for all data included in the analysis.

The definitions and criteria of the other explanatory variables are summarized in **Appendix 2** (Supplementary Information).

3.2.2 Statistical analysis

The associations between the response variable and each of the explanatory variables were assessed using univariable and multivariable logistic regression analysis to calculate the crude OR and 95% CI. In the multivariable logistic regression analysis, we removed therapeutic classification (oncology vs. non-oncology) from the explanatory variables because it showed a high association with the severity of the disease outcome (Cramer's $V > 0.5$). Other explanatory variables did not show a strong association with each other and were included in the multivariable logistic regression analysis. Statistical significance was set at $P < 0.05$. StatsDirect version 3.3.5 software was used for all the statistical analyses.

3.3 Result

A total of 335 drugs with ODD containing new active substances approved in the US between April 1, 2001, and March 31, 2021, were identified. Among these, 233 drugs with ODD were selected for the analysis (**Figure 4**).

The characteristics of the selected orphan drugs are summarized along with the design of the pivotal trial, RCT, or SAT (**Table 3**). Approximately two-thirds of orphan drugs (151 of 233) had a pivotal RCT, and one-third (82 of 233) had a pivotal SAT in the clinical data package. Most drugs (190 of 233) were first approved worldwide. Eighty-one percent of

orphan drugs in SAT targeted high mortality diseases, while 44.4% of the drugs in an RCT targeted high mortality diseases.

Table 4 shows the result of the univariable and multivariable analysis to investigate the associations between the presence or absence of RCT data in the clinical data package and explanatory variables. Univariable analyses demonstrated associations between the presence or absence of RCT data in the clinical data package for NDA in the US and several factors, including (1) the severity of disease outcome, (2) the type of drug usage, and (3) the type of primary endpoint. The result of the multivariable analysis also suggested that severity of disease outcome (OR 5.63, 95% CI 2.64–12.00), type of drug usage (OR 2.95, 95% CI 1.80–18.57), and type of primary endpoint (OR 5.57, 95% CI 2.57–12.06) were associated with the presence or absence of RCT data.

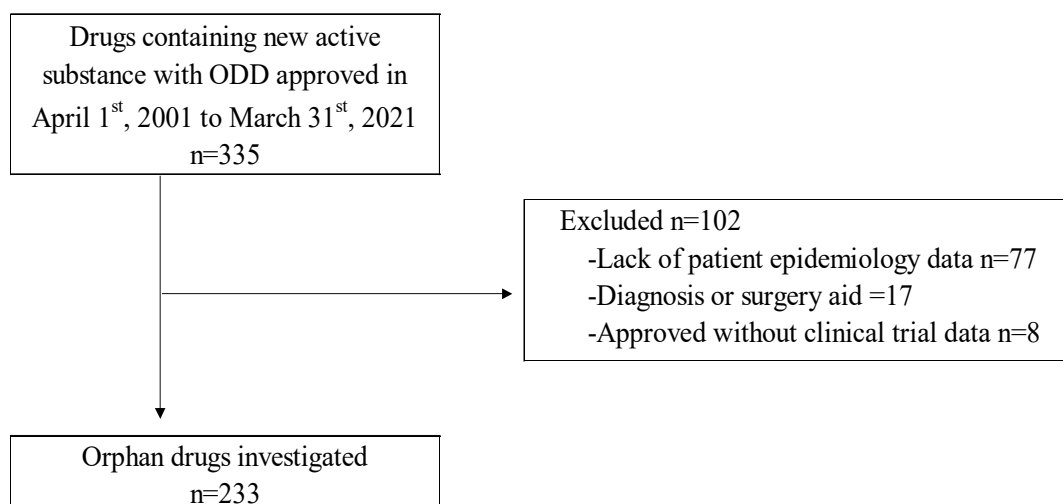


Figure 4 Flow diagram of drug selection (US)

ODD: Orphan Drug Designation

Table 3 Characteristics of orphan drugs (US)

	RCT (n=151)	SAT (n=82)	Total (n=233)
Approval year			
2001-2005	17 (11.3%)	5 (6.1%)	22
2006-2010	18 (11.9%)	9 (11.0%)	27
2011-2015	42 (27.8%)	28(34.1%)	70
2016-2021	74 (49.0%)	40 (48.8%)	114
Prevalence			
1-5 / 10,000	66 (43.7%)	38 (46.3%)	104
1-9 / 100,000	59 (39.1%)	31 (37.8%)	90
1-9 / 1,000,000	21 (13.9%)	6 (7.3%)	27
<1 / 1,000,000	5 (3.3%)	7 (8.5%)	12
Modality			
Chemical	92 (60.9%)	52 (63.4%)	144
Biologics	59 (39.1%)	30 (36.6%)	89
ATC code			
A (Alimentary tract and metabolism)	20 (13.2%)	6 (7.3%)	26
B (Blood and blood forming organs)	20 (13.2%)	9 (11.0%)	29
C (Cardiovascular system)	8 (5.3%)	1 (1.2%)	9
D (Dermatologicals)	2 (1.3%)	0	2
G (Genito urinary system and sex hormones)	0	1 (1.2%)	1
H (Systematic hormonal preparations, excl. sex hormones and insulins)	7 (4.6%)	0	7
J (Antiinfectives for systemic use)	3 (1.3%)	0	3
L (Antineoplastic and immunomodulating agents)	52 (34.4%)	64 (78.0%)	116
M (Musculo-skeletal system)	8 (5.3%)	1 (1.2%)	9
N (Nervous system)	17 (11.3%)	0	17
P (Antiparasitic products, insecticides and repellents)	5 (3.3%)	0	5
R (Respiratory system)	4 (2.6%)	0	4
S (Sensory organs)	3 (2.0%)	0	3
V (Various)	2 (1.3%)	0	2
Target age segment			
Children with or without adult	55 (36.4%)	24 (29.3%)	79
Adult only	96 (63.6%)	58 (70.7%)	154
Primary efficacy endpoint			

Pharmacodynamic/Response biomarker	67 (44.4%)	69 (84.1%)	136
Clinical outcome	84 (55.6%)	13 (15.9%)	97
Severity of the disease outcome			
High mortality	67 (44.4%)	67 (81.7%)	134
Others	84 (55.6%)	15 (18.3%)	99
Prior approval outside of US			
Yes	34 (22.5%)	9 (11.0%)	43
No	117 (77.5%)	73 (89.0%)	190
Alternative treatment in US			
Not available	51 (33.8%)	25 (30.5%)	76
Exists	100 (66.2%)	57 (69.5%)	157
Drug usage			
Mono therapy	128 (84.8%)	78 (95.1%)	206
Combination therapy	23 (15.2%)	4 (4.9%)	27
Designation			
Fast track			
Yes	51 (33.8%)	17 (20.7%)	68
No	100 (66.2%)	65 (79.3%)	165
Breakthrough therapy			
Yes	38 (25.2%)	31 (37.8%)	69
No	113 (74.8%)	51 (62.2%)	164
Priority review			
Yes	87 (57.6%)	52 (63.4%)	139
No	64 (42.4%)	30 (36.6%)	94
Accelerated approval			
Yes	31 (20.5%)	43 (52.4%)	74
No	120 (79.5%)	39 (47.6%)	159

Table 4 Result of univariable and multivariable logistic regression analysis (US)

Factor	RCT (n=151)	SAT (n=82)	Total (n=233)	Univariable regression analysis			Multivariable regression analysis		
				Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Prevalence									
<1/100,000	26 (17.2%)	13 (15.9%)	39	Reference			Reference		
≥1/100,000	125 (82.8%)	69 (84.1%)	194	0.91	0.44-1.88	0.7899	1.31	0.52-3.34	0.561
Severity of the disease outcome									
High mortality	67 (44.4%)	67 (81.7%)	134	Reference			Reference		
Others	84 (55.6%)	15 (18.3%)	99	5.60	2.94-10.68	<0.0001*	5.63	2.64-12.00	<0.0001*
Drug usage									
Mono therapy	128 (84.8%)	78 (95.1%)	206	Reference			Reference		
Combination therapy	23 (15.2%)	4 (4.9%)	27	3.50	1.17-10.51	0.0253*	2.95	1.80-18.57	0.0032*
Target age segment									
Children with or without adult	55 (36.4%)	24 (29.3%)	79	Reference			Reference		
Adult only	96 (63.6%)	58 (70.7%)	154	0.72	0.40-1.29	0.2714	1.72	0.75-3.97	0.2027
Primary efficacy endpoint									
Pharmacodynamic/Response biomarker	67 (44.4%)	69 (84.1%)	136	Reference			Reference		
Clinical outcome	84 (55.6%)	13 (15.9%)	97	6.65	3.39-13.06	<0.0001*	5.57	2.57-12.06	0.0001*
Therapeutic classification									
Oncology	46 (30.5%)	63 (76.8%)	109	Reference			N/A		
Non-oncology	105 (69.5%)	19 (23.2%)	124	7.57	4.08-14.06	<0.0001*			

*P value < 0.05

3.4 Discussion

In this research, we investigated the presence or absence of RCT data in the clinical data package of new drug applications with ODD in the US. We found that the severity of disease outcome, type of drug usage, and type of efficacy endpoint were associated with the presence or absence of RCT data. These results suggest the importance of understanding the target disease and its treatment environment.

Disease severity, defined by high mortality, was positively associated with the absence of RCT data in the package, implying that RCTs are more difficult to conduct in such disease areas. This result was expected because there is no authorized treatment available for most rare diseases [2], and it has been pointed out that it is ethically difficult to conduct a comparative study with a placebo group when there is no standard of care [44]. In such cases, conditional approval based on the totality of evidence with SAT data and other external data under the accelerated approval system may be granted in the US. Although it is necessary to reinforce the evidence through confirmatory trials after conditional approval, early access to treatment options is favorable for the patients suffering from these serious diseases.

Second, the utilization of combination therapy for a test arm showed a positive association with the presence of RCT data. From an ethical perspective, this is another expected result. When the test arm is a combination therapy in which an investigational drug is added to a standard therapy, a standard of care is warranted, which would lower ethical barriers and make it easier to justify conducting RCTs to pursue high-level evidence.

Third, the use of clinical outcomes as an efficacy endpoint was positively associated with the presence of an RCT. This result is similar to that of our previous study using the Japanese data package [47]. In general, biomarkers can be utilized as efficacy endpoints

when an appropriate understanding of the disease has been achieved, and their correlation with the true endpoint has been appropriately justified. Thus, biomarkers based on laboratory test values and radiographic imaging make it possible to obtain early clinical results with a small sample size and lower the possibility of introducing bias [33]. Based on these considerations, it would be natural for clinical trials with smaller sample sizes to be preferred for rare diseases, as it is difficult to secure enough patients to participate in the trials [14,23]. The trend of higher utilization of SAT in the clinical data package of orphan drugs compared to those targeting non-rare diseases is consistent with the results of a previous research [23]. The findings of the present research and our previous research in Japan [47] suggest the importance of this factor in considering the necessity and feasibility of RCTs.

It was unexpected for no association to be found between the disease prevalence and the presence or absence of RCT data. In general, an appropriate sample size is required to conduct an RCT. Thus, we assumed that a lower disease prevalence would be associated with fewer RCTs due to decreased feasibility. In our previous research in Japan, a negative association was confirmed between RCTs and lower prevalence disease prevalence [47]. Although this inconsistency may be due to differences in the drugs targeted in each research, and the sources of disease prevalence may also be attributable, the established multi-regional clinical trial (MRCT) approach in the US may have contributed to enhancing the feasibility of RCTs. The US has an approximately 2.5 times larger population compared to Japan. Thus, the absolute number of target patients would be relatively larger in the US and further increases when MRCT countries are included. As a result, it is speculated that expectations of evidence generation via RCTs are relatively unconstrained by disease prevalence, even in rare diseases in the US. This result is

consistent with previous reports that showed a similar proportion of RCTs over diseases with various prevalence rates [48,49].

This research had several limitations. First, the research was conducted only for approved drugs, which could be regarded as a source of bias. The information available on negative results is less extensive than that available for approved drugs. Second, the data were collected only for drugs that had an ODD. There may be drugs that did not apply for ODD, although they met the ODD criteria. Third, the association between clinical equipoise or natural history data and the presence or absence of RCT data was not investigated. Clinical equipoise is an important ethical consideration for determining the feasibility of RCTs [34], and natural history data are another crucial factor to support the discussion on RCT or SAT from the perspective of totality of evidence in the clinical data package. However, it was difficult to quantify the equipoise and contribution of natural history data to various areas of drugs in this research.

Orphan drugs target various rare diseases with unmet medical needs. If drug development is conducted using SAT data based on sufficient research, discussion, and consideration, it will streamline the development timeline. Thus, patients with rare diseases and unmet medical needs may be afforded early access to these drugs. Conversely, RCTs may impact the feasibility and development period of drug development. However, they are recommended by various guidelines as the results obtained through RCTs are highly reliable and ultimately benefit patients. This argument is unavoidable in orphan drug development, emphasizing the importance of utilizing available evidence.

Our results indicated the importance of selecting a target disease and potential efficacy variables to be used in the clinical trials to examine the need for RCT data for NDA. From a pharmaceutical company perspective, target disease selection is one of the initial steps

in drug development. Preparation of a clinical development plan including pivotal study designs is initiated during this step, which significantly impacts the costs and timelines of drug development, consequently affecting corporate investment decisions. In addition, we believe that strategic collection of relevant information is necessary to establish efficacy variables for potential drug development. This can be achieved through collaboration among the industry, government, and academia, which will help facilitate orphan drug development.

4. Overall Discussions

In both Japan and the US, there has been a common implication of an association between the necessity of RCT data in the clinical data package for orphan drugs and the type of primary endpoint in the pivotal trial. In addition, the association was indicated with disease prevalence in Japan, while in the US, with disease severity and type of drug usage . This suggests that RCT data is needed for drugs when clinical outcomes are used as a primary endpoint of pivotal trials, for drugs for combination therapy, for diseases with relatively less severity, and for diseases with a high prevalence.

While we observed differences in disease prevalence, disease severity, and drug usage between Research 1 in Japan and Research 2 in the US, we understand that the regional differences in considerations about trial design selection are not significant for the following reasons. Regarding the disease prevalence, larger population and growth in the use of multiregional clinical trials in the US may potentially mitigate the impact of low disease prevalence, as opposed to Japan where historically there have been fewer multiregional trials and a relatively smaller population.

Concerning the disease severity, differences in regulatory practice, such as the utilization of expedited approval pathways in the US to allow SAT for severe diseases, might have affected the result. While it is possible that disease severity is given more weight in ethical consideration to discuss clinical trial design in the US, there is no basis or reports suggesting a lack of weight on disease severity in Japan.

The difference in outcomes related to the drug usage is believed to be due to the inability to conduct statistical analysis in Research 1 in Japan, as there were no SAT involving combination therapy drugs. Numerically, like in the US (23 in RCT, 4 in SAT), there were a significant number of RCTs for combination therapy in Japan (14 in RCT, 0 in SAT)

[Table 1, 3].

As stated above, based on the research conducted in both Japan and the US, we have identified several factors that imply a relationship with the necessity of RCT data. Below is a reiteration of the discussions on how each of these factors is linked to the requirement of RCT data.

The positive association between the clinical outcome as a primary endpoint and the necessity of RCT data can be considered as follows. First, it is important to carefully assess the potential bias from both patients and investigators when utilizing clinical outcomes in clinical trials as opposed to biomarkers. This necessitates a thorough and rigorous comparative evaluation in a RCT. Another important consideration is that, for rare diseases, there is often insufficient information on disease progression and efficacy endpoints in clinical trials. These endpoints may be entirely novel or have limited precedents. Therefore, there is a need to rigorously assess clinically meaningful changes through direct comparison with the control group. In contrast, biomarkers like laboratory values or imaging assessments often have established reference values to assess their clinically meaningful changes.

Regarding other factors, it can also be discussed as follows. In terms of the disease prevalence, positive association was implied between high prevalence and the necessity of RCT data. It would be reasonable that diseases with high prevalence make it more feasible to conduct RCTs.

As for the disease severity, negative association was suggested between the severity of the targeted disease and the necessity of RCT data. For rare diseases where standard treatments are often unavailable, ethical concerns would make it difficult to use a placebo as a comparator arm in most cases, especially in severe conditions. In such situations,

SATs may be considered as an alternative, as it ensures access to the active treatment.

Concerning the drug usage, positive association was shown between the combination therapy and the necessity of RCT data. When the investigational arm is a combination therapy in which an investigational drug is added to a standard therapy, a standard of care is warranted as a base treatment, which would lower the ethical barriers and make it easier to justify conducting RCTs.

In light of these considerations, taking into account the unique characteristics of rare diseases and aiming for more accurate efficacy assessment, it is crucial to appropriately examine the necessity of RCT data. For instance, in diseases with relatively high prevalence where clinical outcomes are used for efficacy assessment, there is a higher likelihood of the regulators' requiring RCT data. Such information and predictions would be valuable for a company's development planning. In such cases, identifying a prevalence threshold associated with the necessity of RCT data could provide additional insights into these discussions. However, given the objective of this research, which was to explore factors, qualitative considerations were prioritized.

Based on the results of this research, there are several points that pharmaceutical companies should consider. Firstly, it is important not to readily dismiss the conduct of RCTs due to the challenges posed by the small number of patients. Instead, it is important to choose the most scientifically rigorous efficacy endpoints that can explain how the investigational drug works. If suitable biomarkers have not been clearly established, an evaluation based on clinical outcomes becomes necessary, which increases the necessity of RCT data. Conversely, in cases where reliable biomarkers are available, and the disease has a low prevalence with high severity, SATs may be a viable option.

Secondly, it is crucial to carefully consider these factors from the early stage of

development. To ensure an effective development strategy, it is advisable to avoid initiating development with the assumption of conducting a pivotal SAT and then later discovering the need for RCTs, which could lead to additional investments or project termination. Among the factors identified in this research, prevalence and disease severity are factors that are difficult to control once the development has initiated. Therefore, they should be carefully considered before deciding to proceed with development. On the other hand, efficacy endpoints and drug usage can be modified during the course of development. To reduce the risk of unexpected changes after the start of development, it is desirable to initiate early discussion with the regulatory authorities regarding assessment methods. To facilitate meaningful discussions, it is essential to have information on the pathophysiological mechanisms and disease progression. Conversely, clear understanding of these factors can contribute to improved accuracy of development plan. Therefore, these also should be considered in the early stage of development.

Lastly, on the other hand, the approach mentioned above is feasible for diseases for which information has been accumulated. To fundamentally promote the orphan drug development, it is essential to collect and analyze information on the disease mechanisms and disease progression specific to the target disease. Therefore, establishment of rare disease registries and utilization of real-world data are both valuable tools to consider. Given that these approaches have limitations when relying solely on the efforts of one company, it is essential to acknowledge the importance of comprehensive collaboration between the pharmaceutical industry, governments, and academics.

5. Conclusion

In orphan drug development, emphasis should be placed on the formulation of strategies grounded in the scientific evaluation of the investigational drug and the target disease, rather than solely on the feasibility of conducting trials based on the small number of patients. To minimize the risk of unforeseen changes in the development plan and to optimize the development strategy and investment, it is advisable for pharmaceutical companies to engage in early discussions with the regulatory authorities regarding efficacy assessment methods based on the accurate collection and analysis of foundational information. Furthermore, it is important to collaborate among the pharmaceutical industry, academia, and government to establish disease registries and enhance the usability of real-world data, as clarifying the pathophysiological mechanisms and progression of diseases can contribute to supporting orphan drug development. We hope our research will contribute to optimize the drug development plan through enhancing the predictability of the necessity of RCT data for NDA and also encourage strategic collection of the target disease information to promote future orphan drug development.

References

1. Haendel M, Vasilevsky N, Unni D, et al. How many rare diseases are there? *Nat Rev Drug Discov.* 2020;19(2):77-8.
2. Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. *Orphanet J Rare Dis.* 2023;18(1):163. doi.org/10.1186/s13023-023-02790-7
3. Rare Diseases at FDA. <https://www.fda.gov/patients/rare-diseases-fda> The current as of: 09/21/2022
4. Miller KL, Fermaglich LJ, Maynard J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet J Rare Dis.* 2021;16:265. doi: 10.1186/s13023-021-01901-6.
5. Sakushima K, Takeda H, Aoi Y. Orphan drug designation and development in Japan: 25 years of experience and assessment. *Nat Rev Drug Discov.* 2021;20:893–4.
6. Murakami M, Narukawa M. Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. *Drug Discov Today.* 2016;21:544–9.
7. Erik T, Benjamin V, Christopher PA, et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nature Reviews Drug Discovery.* 2020;19, 93–111.

8. Pontes C, Fontanet JM, Vives R, et al. Evidence supporting regulatory-decision making on orphan medicinal products authorization in Europe: methodological uncertainties. *Orphanet J Rare Dis.* 2018;13:206. doi: 10.1186/s13023-018-0926-z.
9. Bessalov A, Wicke K, Castagne V. Blinding and randomization. *Handb Exp Pharmacol.* 2020;257:81–100.
10. Gore SM. Assessing clinical trials—why randomise? *Br Med J (Clin Res Ed).* 1981;282:1958–60.
11. Sverdllov O, Rosenberger WF. Randomization in clinical trials: can we eliminate bias? *Clin Invest.* 2012;3:37–47.
12. Preventive Services Task Force. Guide to clinical preventive services: report of the U.S. Preventive Services Task Force. 2nd ed. Baltimore: Williams & Wilkins; 1996. <https://www.ncbi.nlm.nih.gov/books/NBK61778/>
13. Feinstein AR. Current problems and future challenges in randomized clinical trials. *Circulation.* 1984;70:767–74.
14. Day S, Jonker AH, Lau LPL, et al. Recommendations for the design of small population clinical trials. *Orphanet J Rare Dis.* 2018;13:195. doi: 10.1186/s13023-018-0931-2.
15. Nony P, Kurbatova P, Bajard A, et al. A methodological framework for drug development in rare diseases. *Orphanet J Rare Dis.* 2014;9:164. doi: 10.1186/s13023-014-0164-y.
16. Tamura RN, Krischer JP, Pagnoux C, et al. A small n sequential multiple assignment randomized trial design for use in rare disease research. *Contemp Clin Trials.* 2016;46:48–51.

17. Gupta S, Faughnan ME, Tomlinson GA, et al. A framework for applying unfamiliar trial designs in studies of rare diseases. *J Clin Epidemiol*. 2011;64:1085–94.
18. Whicher D, Philbin S, Aronson N. An overview of the impact of rare disease characteristics on research methodology. *Orphanet J Rare Dis*. 2018;13:14. doi: 10.1186/s13023-017-0755-5.
19. Balevic SJ, Cohen-Wolkowicz M. Innovative study designs optimizing clinical pharmacology research in infants and children. *J Clin Pharmacol*. 2018;58(Suppl 10):S58–72.
20. Feinberg BA, Gajra A, Zettler ME, et al. Use of real-world evidence to support FDA approval of oncology drugs. *Value Health*. 2020;23:1358–65.
21. Wu J, Wang C, Toh S, et al. Use of real-world evidence in regulatory decisions for rare diseases in the United States—current status and future directions. *Pharmacoepidemiol Drug Saf*. 2020;29:1213–8.
22. Goring S, Taylor A, Muller K, et al. Characteristics of non-randomised studies using comparisons with external controls submitted for regulatory approval in the USA and Europe: a systematic review. *BMJ Open*. 2019;9:e024895. doi: 10.1136/bmjopen-2018-024895.
23. Bell SA, Smith CT. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet J Rare Dis*. 2014;9:170. doi: 10.1186/s13023-014-0170-0.
24. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Rare Diseases: Common Issues in Drug

- Development. Guidance for Industry.
- <https://www.fda.gov/media/119757/download>. Accessed 5 June 2021.
25. European Medicines Agency. Guideline on Clinical Trials in Small Populations.
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf. Accessed 5 June 2021.
26. Rachel S, Kathleen D, Melissa R, Nina H, et al. Accelerating development of scientific evidence for medical products within the existing US regulatory framework. *Nat Rev Drug Discov*. 2017;16(5):297–8.
27. Maeda K, Kaneko M, Narukawa M, et al. Points to consider: efficacy and safety evaluations in the clinical development of ultra-orphan drugs. *Orphanet J Rare Dis*. 2017;12:143. doi: 10.1186/s13023-017-0690-5.
28. Pariser AP, Slack JD, et al. Characteristics of rare disease marketing applications associated with FDA product approvals 2006-2010. *Drug Discov Today*. 2012 ;17(15-16):898-904.
29. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2020. https://www.whocc.no/atc_ddd_index/. Accessed 5 June 2021.
30. Ministry of Health, Labour and Welfare. Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs (in Japanese).
- <https://www.mhlw.go.jp/stf/shingi/other-iyaku128701.html>. Accessed 5 June 2021.
31. Harrell Jr. FE, Lee KL; Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996; 15(4): 361–87.

32. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein, AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology*. 1996; 49(12): 1373–9.
33. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Published January 28, 2016; Last Update: January 25, 2021.
34. Freedman B. Equipoise and the Ethics of Clinical Research. *N Engl J Med*. 1987;317:141-5.
35. Maeda H, Kurokawa T. The history of developing anticancer drugs and their evaluation guidelines in Japan. *Yakushigaku Zasshi* 2014;49:196–204.
36. Cox GF. The art and science of choosing efficacy endpoints for rare disease clinical trials. *Am J Med Genet A*. 2018;176:759–772.
37. Michael T, Jurgens H, et al. FDA approval, clinical trial evidence, efficacy, epidemiology, and price for non-orphan and ultra-rare, rare, and common orphan cancer drug indications: cross sectional analysis. *BMJ* 2023;381:e073242. doi: 10.1136/bmj-2022-073242.
38. US Food and Drug Administration. Orphan Drug Act—Relevant Excerpts.
<https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products>
39. Orphan Drug. Act of 1983. Pub L. No. 97–414, 96 Stat. 2049.
40. Anthony H, Marilyn C, et al. The current status of orphan drug development in Europe and the US. *Intractable Rare Dis Res*. 2014;3(1):1–7.
41. Nina H, Gayatri R, Rachel S, et al. Flexibility in the FDA approach to orphan drug development. *Nat Rev Drug Discov*. 2017;16(11):737–8.

42. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Rare Diseases: Common Issues in Drug Development. Guidance for Industry.
<https://www.fda.gov/media/119757/download>. Accessed 5 November 2022.
43. European Medicines Agency. Guideline on Clinical Trials in Small Populations.
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf. Accessed 5 November 2022.
44. Gaasterland CM, Jansen-van der Weide MC, du Prie-Olthof MJ, et al. The patient's view on rare disease trial design – a qualitative study. *Orphanet J Rare Dis.* 2019;14:31. doi: 10.1186/s13023-019-1002-z.
45. Meulemeester JD, Fedyk M, Jurkovic L, et al. Many randomized clinical trials may not be justified: a cross-sectional analysis of the ethics and science of randomized clinical trials. *J Clin Epidemiol.* 2018;97:20–5.
46. Gerss JW, Köpcke W. Clinical trials and rare diseases. *Adv Exp Med Biol.* 2010;686:173–190.
47. Kubota Y, Narukawa M. Randomized Controlled Trial Data for New Drug Application for Rare Diseases in Japan. *Therapeutic Innovation & Regulatory Science* 2022;56:659–66
48. Siew H, Adrian W, Catrin S et al. Does the low prevalence affect the sample size of interventional clinical trials of rare diseases? An analysis of data from the aggregate analysis of clinicaltrials.gov. *Orphanet J Rare Dis.* 2017;12(1):44. doi: 10.1186/s13023-017-0597-1.

49. Himabindu G, Ke L, Anne P et al. Rare cancer trial design: lessons from FDA approvals. Clin Cancer Res. 2012;18(19):5172-8.

Acknowledgement

I would like to convey my profound gratitude to my supervisor, Professor Mamoru Narukawa, for his steadfast guidance, patience, and support throughout my doctoral research. His wealth of knowledge, expertise, and unwavering commitment to my success have been invaluable to me.

I would also like to extend my sincere thanks to my committee members, Professor Kenichi Negishi, Professor Mitsuo Tanabe, and Associate Professor Mitsuhiro Sugawara, for their insightful feedback and constructive comments that have helped shape this work. I am grateful to Ms. Yukiko Minami for her invaluable support and guidance in managing my PhD course, as well as to my colleagues in Kitasato university and Astellas Pharma Inc. for their engaging conversations, helpful suggestions, and continuous support.

Finally, I would like to express my heartfelt gratitude to my wife and daughter for their unwavering love and support. They have been a constant source of encouragement and inspiration throughout this journey. Without them, this achievement would not have been possible.

Appendix 1: Definition and information sources of each factor (Research 1, Japan)

1. Disease prevalence in Japan (<1/100,000 vs. ≥1/100,000)

The number of patients for target drugs in Japan was obtained from the proceedings of the Pharmaceutical Affairs and Food Sanitation Council Special Committee (<https://www.mhlw.go.jp/stf/shingi/indexshingi.html>), review reports and minutes of Pharmaceutical Affairs and Food Sanitation Council First/Second Committee on Drugs. The largest estimated number among these sources were selected and it was divided by Japanese national population (125 million) in 2021 to calculate disease prevalence. The calculated prevalence was categorized into 1<1,000,000, 1-9/1,000,000, 1-9/100,000, and 1-5/10,000 based on the Orphanet range (<http://www.orphadata.org/cgi-bin/epidemio.html>). For the statistical analysis, these categories were categorized into <1/100,000 vs. ≥1/100,000.

2. Alternative treatment in Japan (Not available vs. Exists)

Information about the availability of alternative treatment options for the target indication in Japan was investigated based on the data available on the PMDA website (<https://www.pmda.go.jp/PmdaSearch/iyakuSearch/>).

3. Therapeutic area (Oncology vs Non-oncology)

The approved medicines were categorized into oncology or non-oncology based on the ATC codes.

4. Patient age segment (Children with or without adult vs. adult only)

The diseases were categorized as “Adults and Children” (diseases affecting adults and children or children only) and “Adult only” (diseases affecting adults only). If in the package insert, under “Indications”, “Dosage and Administration” or “Pediatric Use”, there is an indication of their applicability to children, the drug is categorized as “Adult and Children.”

Appendix 2: Definition and information sources of each factor (Research 2, the US)

1. Disease prevalence (<1/100,000 vs. ≥1/100,000)

The disease prevalence of patient-targeted drugs was obtained from Orphanet (<https://www.orpha.net/consor/cgi-bin/index.php>) and the Surveillance, Epidemiology, and End Results (<https://seer.cancer.gov/>). Additionally, the number of patients for target drugs was obtained from review reports and divided by the United States national population (3.32 million) in 2022 to calculate the disease prevalence.

The largest estimated disease prevalence among these sources was selected in case of conflict. Disease prevalence was categorized into < 1/1,000,000, < 1–9/1,000,000, < 1–9/100,000, and < 1–5/10,000 based on the Orphanet range (<http://www.orphadata.org/cgi-bin/epidemio.html>). For statistical analysis, these categories were categorized as < 1/100,000 versus ≥ 1/100,000.

2. Therapeutic area (Oncology vs Non-oncology)

The approved medicines were categorized into *oncology* or *non-oncology* based on ATC codes.

3. Patient age segment (Children with or without adult vs. adult only)

Diseases were categorized as *Adults and Children* (diseases affecting adults and children or children only) and *Adult only* (diseases affecting adults only). If in the package insert, under *Indications*, *Dosage and Administration*, or *Pediatric Use*, there is an indication of their applicability to children, the drug is categorized under *Adult and Children*.